4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 73

[Docket No. FDA-2020-C-2131]

Listing of Color Additives Exempt from Certification; Jagua (Genipin-Glycine) Blue

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or we) is amending the color additive regulations to provide for the safe use of jagua (genipin-glycine) blue as a color additive in various food categories at levels consistent with good manufacturing practice (GMP). We are taking this action in response to a color additive petition (CAP) submitted by Exponent, Inc. on behalf of Ecoflora SAS (Ecoflora).

DATES: This rule is effective [INSERT DATE 30 DAYS PLUS 1 BUSINESS DAY AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. See section X for further information on the filing of objections. Either electronic or written objections and requests for a hearing on the final rule must be submitted by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit objections and requests for a hearing as follows. Please note that late, untimely filed objections will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Objections received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic objections in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Objections submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your objection will be made public, you are solely responsible for ensuring that your objection does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your objection, that information will be posted on https://www.regulations.gov.
- If you want to submit an objection with confidential information that you do not wish to be made available to the public, submit the objection as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand Delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper objections submitted to the Dockets Management Staff, FDA will post your objection, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2020-C-2131 for "Listing of Color Additives Exempt from Certification; Jagua (Genipin-Glycine) Blue." Received objections, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at

https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions-- To submit an objection with confidential information that you do not wish to be made publicly available, submit your objections only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." We will review this copy, including the claimed confidential information, in our consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Shayla West-Barnette, Center for Food Safety and Applied Nutrition, Food and Drug Administration, 5001 Campus Dr., College Park, MD 20740-3835, 240-402-1262.

SUPPLEMENTARY INFORMATION:

I. Introduction

In a notification published in the *Federal Register* on November 20, 2020 (85 FR 74304), we announced that we filed a color additive petition (CAP 0C0317) submitted by Ecoflora SAS, c/o Exponent, Inc., 1150 Connecticut Ave. NW, Suite 1100, Washington, DC 20036. The petition proposed to amend the color additive regulations in part 73 (21 CFR part 73), "Listing of Color Additives Exempt from Certification," to provide for the safe use of jagua (genipin-glycine) blue, derived from the pulp of the unripe jagua fruit (*Genipa americana*), as a color additive at levels consistent with GMP in flavored milk; dairy drinks and substitutes; dairy and dairy alternative yogurt; ice cream, frozen dairy and dairy alternative desserts, puddings, gelatins, ices, sorbets; ready-to-eat multicolored cereals; flavored potato chips, tortilla, corn, and other chips; candy and chewing gum; non-alcoholic fruit based/flavored drinks, nutritional beverages and smoothies; flavored cream cheese-based spreads; and icings, frostings, jams, syrups, and fruit toppings and fillings.

II. Background

The color additive that is the subject of this petition is a dark blue liquid or powder produced by reacting genipin (CAS Reg. No. 6902-77-8) in the juice of the unripe fruit of *Genipa americana* with an equivalent amount of the amino acid glycine (CAS Reg. No. 56-40-6) using mild heat. The principal coloring component in jagua (genipin-glycine) blue is a genipin-glycine polymer (CAS Reg. No. 1314879-21-4) consisting of repeating dimeric units containing two genipin moieties reacted to add glycine units as side chains. We will subsequently refer to this principal coloring component as "the polymer." Iridoids, of which genipin is an example, are found in a wide variety of plants, and glycine is a common building block of proteins. The color additive jagua (genipin-glycine) blue also contains three dimers as minor coloring components (CAS Reg. No. 1313734-13-2, CAS Reg. No. 104359-67-3, and CAS Reg. No. 1313734-14-3) that are structural units of the polymer.

The petitioner proposed the following specifications for jagua (genipin-glycine) blue: appearance, dark blue; color value (E10 percent), 240-280 for the powder form and 120-240 for the liquid form; polymer, 20 to 40 percent for the powder form and 10 to 35 percent for the liquid form; aflatoxins (B1, B2, G1, and G2), not more than 0.01 milligram per kilogram (mg/kg); fumonisine (B1, B2), not more than 0.5 mg/kg; *Escherichia coli*, negative in 1 gram (g); aerobic plate count, not more than 1,000 colony forming units per gram (cfu/g); yeast and mold, not more than 300 cfu/g, and *Staphylococcus aureus*, negative in 1 g.

FDA amended the proposed specifications to add the following: arsenic, not more than 1 mg/kg; cadmium, not more than 1 mg/kg; mercury, not more than 1 mg/kg; and lead, not more than 1 mg/kg (Ref. 1). We also amended the proposed specification for genipin, not more than 20 mg/kg, to be consistent with the petitioner's analytical results. Furthermore, we concluded that the petitioner's proposed specifications for appearance, color value, polymer, glycine, the minor coloring components, carbohydrate, modified starch, total fat, total protein, and ash content are not needed in the codified regulation (Ref. 1).

III. Safety Evaluation

Under section 721(b)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 379e(b)(4)), a color additive may not be listed for a proposed use unless the data and information available to FDA establish that the color additive is safe for that use. Our color additive regulations at 21 CFR 70.3(i) define "safe" to mean that there is convincing evidence establishing with reasonable certainty that no harm will result from the intended use of the color additive.

To determine whether a color additive is safe under the general safety clause, the FD&C Act requires FDA to conduct a fair evaluation of the available data and consider, among other relevant factors: (1) probable consumption of, or other relevant exposure from, the additive and of any substance formed in or on food, drugs, devices, or cosmetics because of the use of the additive; (2) cumulative effect, if any, of such additive in the diet of man or animals, taking into

account chemically or pharmacologically related substance or substances in such diet; and (3) safety factors recognized by experts as appropriate for the use of animal experimentation data (see section 721(b)(5)(A)(i) through (iii) of the FD&C Act).

As part of our safety evaluation to establish with reasonable certainty that a color additive is not harmful under its intended conditions of use, we consider the additive's manufacturing and stability, the projected human dietary exposure to the additive and any impurities resulting from the petitioned use of the additive, the additive's toxicological data, and other relevant information (such as published literature) available to us.

IV. Safety of the Petitioned Use of the Color Additive

A. Dietary Exposure Estimate

The petitioner requested that jagua (genipin-glycine) blue be permitted at levels consistent with GMP and provided the representative maximum use levels for the color additive for each proposed food use. The petitioner used food consumption data from the 2013-2016 National Health and Nutrition Examination Survey (NHANES) to estimate the dietary exposure to jagua (genipin-glycine) blue and to the polymer from the proposed uses. The petitioner stated that the use of the liquid form of jagua (genipin-glycine) blue would be substitutional for the powder form and that, on the polymer basis, the use levels are the same for both forms.

The petitioner estimated the eaters-only (i.e., only those individuals in the population that consume the foods of interest) dietary exposure to jagua (genipin-glycine) blue to be 34 mg/person/day (mg/p/d) at the mean and 78 mg/p/d at the 90th percentile for the U.S. population aged 2 years and older, and 34 mg/p/d at the mean and 76 mg/p/d at the 90th percentile for children aged 2 to 5 years.

The petitioner provided a specification limit of 20 to 40 percent for the polymer in jagua (genipin-glycine) blue powder. We estimated the eaters-only dietary exposure to the polymer to be 14 mg/p/d at the mean and 31 mg/p/d at the 90th percentile for the U.S. population aged 2

years and older, and 14 mg/p/d at the mean and 30 mg/p/d at the 90th percentile for children aged 2 to 5 years (Ref. 2).

B. Toxicological Considerations

To establish that jagua (genipin-glycine) blue is safe for consumption at the proposed levels, the petitioner used aqueous jagua (genipin-glycine) blue containing a specified percentage of the polymer to conduct the following studies: (1) bacterial reverse mutation assay, mouse lymphoma assay, and in vitro mouse micronucleus assay addressing potential mutagenicity and genotoxicity of the polymer; (2) studies conducted in rats to address the potential toxic effects of acute oral exposure to the polymer; (3) 28-day oral toxicity studies in rats and beagle dogs and 90-day repeated dose oral toxicity studies in rats and beagle dogs to address the potential toxic effects of subchronic oral exposure to the polymer; and (4) 12 months repeated dose toxicity study including in utero exposure in rats to address the potential toxic and/or reproductive effects of chronic oral exposure to the polymer.[1] FDA searched the publicly available literature to identify any new studies that might have examined toxicological effects of jagua (genipin-glycine) blue, or genipin or related compounds; however, no relevant studies were found.

We reviewed the mutagenicity and genotoxicity studies (a bacterial reverse mutation assay, an in vitro mouse lymphoma, and an in vivo mammalian micronucleus induction assay) and concluded that the polymer is not mutagenic or genotoxic under the experimental procedures and conditions applied (Ref. 3).

We reviewed the acute oral toxicity studies and concluded that the oral median lethal dose is greater than 661 mg/kg body weight (bw) of the polymer for the female rats used in the study (Ref. 3).

We reviewed the 28-day studies conducted in rats and in beagle dogs and consider these only as range-finding studies due to the limited number of animals tested per group and other

[1] The polymer content of the test material used for toxicological studies varied slightly from batch to batch; therefore, the toxicological evaluation of studies and the resulting safety conclusions were based on the polymer content of the batch used.

study limitations, and thus not appropriate to establish a no-observed-effect-level (NOEL) or no-observed-adverse-effect-level (NOAEL). We reviewed the 90-day repeated dose oral toxicity study conducted in rats and concur with the study authors that the NOAEL for the rats under the conditions of the study was 330.5 mg/kg bw/d of the polymer for both sexes of the rats. We also reviewed the 90-day repeated dose oral toxicity study in dogs; however, due to the low number of dogs tested per group, and other inadequacies and limitations in the experimental design, we concluded that a NOAEL for the polymer could not be established from this study (Ref. 3).

We reviewed the 12-months repeated dose toxicity study including in utero exposure in rats. The lowest of all the NOAELs for F_0 (parental) generation male rats was 1,127 mg/kg bw/d of polymer[2] (Ref. 3).

The study chosen to establish an acceptable daily intake (ADI) for the polymer was the 12 months repeated dose toxicity study including in utero exposure to rats over the 90-day study in rats. This study combined the in utero phase and a 1-year chronic toxicity phase of sufficient length and overall complexity to produce information on chronic exposure to the polymer. Based on the NOAEL of the polymer (1,127 mg/kg bw/d)) in the 12 months repeated dose toxicity study in rats including in utero exposure, and applying a safety factor of 500 (10 to account for possible increased sensitivity of humans compared to test animals, 10 to account for sensitive individuals in determining safe intake for humans, and 5 for the lack of metabolism and pharmacokinetics and long-term chronic study), the ADI for the polymer is calculated as follows: 1,127 mg/kg bw/d (NOAEL)/500 = 2.3 mg/kg bw/d or 138 mg/p/d (based upon 60 kg bw/p) (Ref. 3).[3]

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[2] The NOAEL of the polymer (1,127 mg/kg bw/d) was derived from the NOAEL of the test material (3,094.7 mg/kg bw/d) used in the study. The polymer content of this test material was 36.4 percent. The NOAEL of the polymer (1,127 mg/kg bw/d) = NOAEL of the test material (3,094.7 mg/kg bw/d) x 0.364 = 1,127 mg/kg bw/d.

[3] The Joint Expert Committee on Food Additives (2020) (Ref. 4) evaluated the 12 months repeated dose toxicity study including in utero exposure in rats with jagua (genipin-glycine) blue and reported that the dietary exposure of jagua (genipin-glycine) blue did not produce any treatment-related effects in this study. Therefore, the committee identified a NOAEL of 3,094.7 mg/kg bw/d (1,127 mg/kg bw/d based on 36.4 percent polymer content) and no effects observed in F0 parental male rats.

The petitioner estimated the highest dietary exposure (37 mg/p/d at 90th percentile based on the polymer) for children aged 6-12 years as well as adolescents aged 13-18 years. The highest estimated dietary exposure value of 37 mg/p/d at the 90th percentile based on the polymer is lower than the ADI value of 138 mg/p/d polymer.

Therefore, we conclude that the proposed use of jagua (genipin-glycine) blue as a color additive at levels consistent with GMP is considered to have reasonable certainty of no harm (Ref. 3).

V. Conclusion

Based on the data and information in the petition and other available relevant information, we conclude that the petitioned use of jagua (genipin-glycine) blue as a color additive in flavored milk; dairy drinks and substitutes; dairy and dairy alternative yogurt; ice cream, frozen dairy and dairy alternative desserts, puddings, gelatins, ices, sorbets; ready-to-eat multicolored cereals, flavored potato chips, tortilla, corn, and other chips; candy and chewing gum; non-alcoholic fruit based/flavored drinks, nutritional beverages and smoothies; flavored cream cheese-based spreads; and icings, frostings, jams, syrups, and fruit toppings and fillings, provided the amount of jagua (genipin-glycine) blue does not exceed levels consistent with GMP.

We further conclude that this color additive will achieve its intended technical effect and is suitable for the petitioned use. Therefore, we are amending the color additive regulations in part 73 to provide for the safe use of this color additive as set forth in this document. In addition, based on the factors in 21 CFR 71.20(b), we conclude that batch certification of jagua (genipin-glycine) blue is not necessary to protect the public health.

VI. Public Disclosure

In accordance with § 71.15 (21 CFR 71.15), the petition and the documents that we considered and relied upon in reaching our decision to approve the petition will be made available for public disclosure (see **FOR FURTHER INFORMATION CONTACT**). As

provided in § 71.15, we will delete from the documents any materials that are not available for public disclosure.

VII. Analysis of Environmental Impact

As stated in the November 20, 2020, *Federal Register* notice of filing, the petitioner claimed that this action is categorically excluded under § 25.32(k) (21 CFR 25.32(k)) because jagua (genipin-glycine) blue would be added directly to food and is intended to remain in the food through ingestion by consumers and is not intended to replace macronutrients in food. We further stated that if FDA determines a categorical exclusion applies, neither an environmental assessment nor an environmental impact statement is required. We did not receive any new information or comments regarding this claim of categorical exclusion. We considered the petitioner's claim of categorical exclusion and determined that this action is categorically excluded under § 25.32(k). Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Paperwork Reduction Act of 1995

This final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

IX. Section 301(ll) of the FD&C Act

Our review of this petition was limited to section 721 of the FD&C Act. This final rule is not a statement regarding compliance with other sections of the FD&C Act. For example, section 301(ll) of the FD&C Act (21 U.S.C. 331(ll)) prohibits the introduction or delivery for introduction into interstate commerce of any food that contains a drug approved under section 505 of the FD&C Act (21 U.S.C. 355), a biological product licensed under section 351 of the Public Health Service Act (42 U.S.C. 262), or a drug or biological product for which substantial clinical investigations have been instituted and their existence has been made public, unless one of the exemptions in section 301(ll)(1) to (4) of the FD&C Act applies. In our review of this petition, we did not consider whether section 301(ll) of the FD&C Act or any of its exemptions

apply to food containing this color additive. Accordingly, this final rule should not be construed to be a statement that a food containing this color additive, if introduced or delivered for introduction into interstate commerce, would not violate section 301(ll) of the FD&C Act. Furthermore, this language is included in all color additive final rules that pertain to food and therefore should not be construed to be a statement of the likelihood that section 301(ll) of the FD&C Act applies.

X. Objections

This rule is effective as shown in the **DATES** section, except as to any provisions that may be stayed by the filing of proper objections. If you will be adversely affected by one or more provisions of this regulation, you may file with the Dockets Management Staff (see **ADDRESSES**) either electronic or written objections. You must separately number each objection, and within each numbered objection you must specify with particularity the provision(s) to which you object, and the grounds for your objection. Within each numbered objection, you must specifically state whether you are requesting a hearing on the particular provision that you specify in that numbered objection. If you do not request a hearing for any particular objection, you waive the right to a hearing on that objection. If you request a hearing, your objection must include a detailed description and analysis of the specific factual information you intend to present in support of the objection in the event that a hearing is held. If you do not include such a description and analysis for any particular objection, you waive the right to a hearing on the objection.

Any objections received in response to the regulation may be seen in the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, and will be posted to the docket at https://www.regulations.gov. We will publish notice of the objections that we have received or lack thereof in the *Federal Register*.

XI. References

The following references marked with an asterisk (*) are on display at the Dockets Management Staff (see **ADDRESSES**) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at https://www.regulations.gov. References without asterisks are not on public display at https://www.regulations.gov because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. *Memorandum from N. Belai, Division of Color Certification and Technology, Office of Cosmetics and Colors, Color Technology Branch to Division of Food Ingredients, Office of Food Additive Safety, Regulatory Review Branch, Team 1, Attention: Shayla West-Barnette, August 16, 2023.

2. *Memorandum from R. Kolanos, Division of Food Ingredients, Chemistry Review Group 2, Office of Food Additive Safety to Division of Food Ingredients, Regulatory Review Group 2, Attention: S. West-Barnette, August 7, 2023.

3. *Memorandum from Abu T. Khan, Office of Food Additive Safety, Division of Food Ingredients, to Mical Honigfort, Regulatory Review Branch, Office of Food Additive Safety, Division of Food Ingredients, August 16, 2023.

4. Food Agriculture Organization of the United Nations (FAO)/World Health Organization (WHO) Joint Expert Committee on Food Additives, Summary and Conclusions of Virtual Meeting, issued on July 10, 2020.

List of Subjects in 21 CFR Part 73

Color additives, Cosmetics, Drugs, Foods, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under the authority delegated to the Commissioner of Food and Drugs, 21 CFR part 73 is amended as follows:

PART 73--LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION

1. The authority citation for part 73 continues to read as follows:

Authority: 21 U.S.C. 321, 341, 342, 343, 348, 351, 352, 355, 361, 362, 371, 379e.

2. Add § 73.225 to subchapter A to read as follows:

§ 73.225 Jagua (genipin-glycine) blue.

(a) *Identity*. (1) The color additive jagua (genipin-glycine) blue is a dark blue powder or liquid prepared from the juice of the unripe fruit of *Genipa americana* by reacting the genipin in the juice with glycine using mild heat. The color additive contains a polymer as the principal coloring component and three dimers as minor coloring components.

(2) Color additive mixtures for food use made with jagua (genipin-glycine) blue may contain only those diluents that are suitable and are listed in this subpart as safe for use in color additive mixtures for coloring foods.

(b) *Specifications*. Jagua (genipin-glycine) blue must conform to the following specifications and must be free from impurities, other than those named, to the extent that such other impurities may be avoided by good manufacturing practice:

(1) Arsenic, not more than 1 milligram/kilogram (mg/kg) (1 part per million (ppm)).

(2) Cadmium, not more than 1 mg/kg (1 ppm).

(3) Lead, not more than 1 mg/kg (1 ppm).

(4) Mercury, not more than 1 mg/kg (1 ppm).

(5) Genipin, not more than 20 mg/kg (20 ppm).

(c) *Uses and restrictions*. Jagua (genipin-glycine) blue may be safely used for coloring flavored milk; dairy drinks and substitutes; dairy and dairy alternative yogurt; ice cream, frozen dairy and dairy alternative desserts, puddings, gelatins, ices, sorbets; ready-to-eat multicolored cereals; flavored potato chips, tortilla, corn, and other chips; candy and chewing gum; non-alcoholic fruit based/flavored drinks, nutritional beverages and smoothies; flavored cream cheese-based spreads; and icings, frostings, jams, syrups, and fruit toppings and fillings at levels consistent with good manufacturing practice, except that it may not be used for coloring foods

for which standards of identity have been issued under section 401 of the Federal Food, Drug, and Cosmetic Act, unless the use of added color is authorized by such standards.

(d) *Labeling requirements*. The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes must conform to the requirements of § 70.25 of this chapter.

(e) *Exemption from certification*. Certification of this color additive is not necessary for the protection of the public health and therefore batches thereof are exempt from the certification requirements of section 721(c) of the Federal Food, Drug, and Cosmetic Act.

Dated: October 30, 2023.

Lauren K. Roth,

Associate Commissioner for Policy.

[FR Doc. 2023-24352 Filed: 11/2/2023 8:45 am; Publication Date: 11/3/2023]